

Enyne Cross-Metathesis with Strained, Geminally-Substituted Alkenes: Direct Access to Highly Substituted 1,3-Dienes

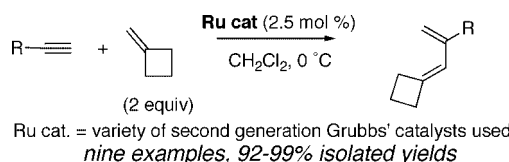
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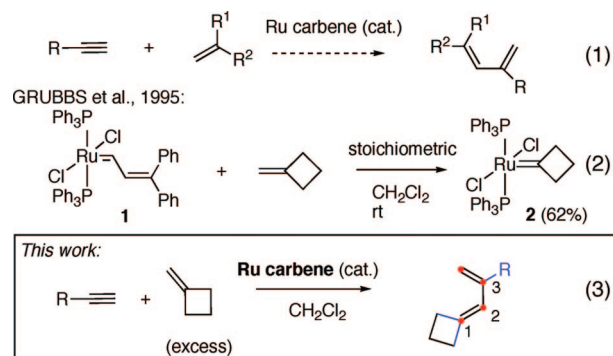
ABSTRACT



Angle strain in methylene cyclobutane was used to drive a cross-ene metathesis with 1-alkynes, giving 1,1,3-trisubstituted 1,3-dienes in good isolated yields. An extensive survey of Grubbs' second-generation catalysts led to an optimized reaction conducted at 0 °C.

Enyne metathesis has become a useful method for carbon–carbon bond formation.¹ In its most commonly used form, the intermolecular (cross) enyne metathesis² between 1-alkene and an alkyne generates a 1,3-diene with the 1,3-disubstitution pattern ($R^1 = H$, eq 1, Scheme 1). Although enyne metathesis is often compared to alkene metathesis, there is one notable difference: in cross alkene metathesis, geminal alkenes can be crossed with 1-alkenes to give trisubstituted alkene products.³ Knowing this, it seems like trisubstituted dienes of the 1,1,3-trisubstitution pattern should be accessible from geminally-substituted alkenes (eq 1, Scheme 1). However, 1,1-disubstituted alkenes display poor reactivity with the Grubbs catalyst. Because the enyne metathesis is believed to occur by an “alkylidene-first” mechanism,⁴ the alkene is required to react with the

Scheme 1. Strained Alkenes Undergo Cross Metathesis



(1) Enyne reviews: (a) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1–18. (b) Mori, M. Ene-Yne Metathesis. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003; Vol. 2, pp 176–204. (c) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317–1382.

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catalyst to form the needed alkylidene. In this paper, we show that angle strain in methylene cyclobutane can effectively drive the cross enyne metathesis, giving rise to dienes of 1,1,3-trisubstitution pattern in a single catalytic metathesis step (eq 3, Scheme 1).

There is limited data on geminal alkene reactivity in metathesis. Strain in a geminal alkene can be used to drive the alkene initiation step. Examination of the literature provides two examples of geminal alkenes that were shown to form ruthenium

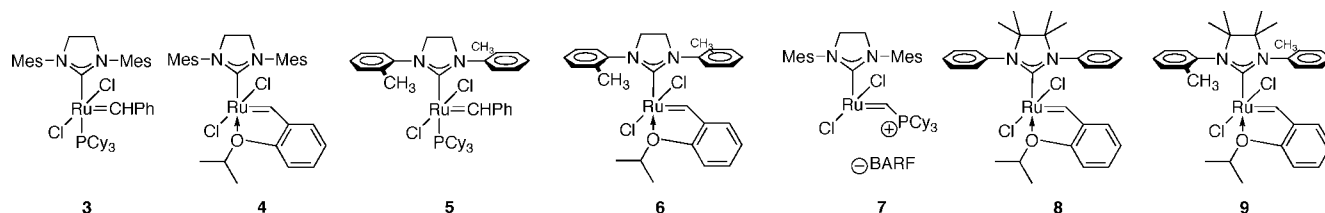


Figure 1. Grubbs' catalysts used in this study.

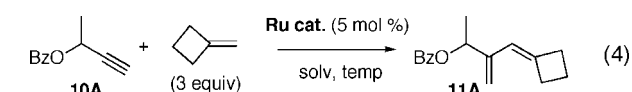
carbenes. In 1995, the Grubbs group showed that the neophylidene complex **1** reacted with both methylene cyclopropane and methylene cyclobutane (eq 2, Scheme 1).⁵ The Caltech group structurally characterized the geminally-substituted metal carbene **2** derived from methylene cyclobutane. We took this as a positive indication that the strain release on going to the spiro metallacycle could be used to effect initiation in the second generation Grubbs carbenes with the (H₂IMes)(L)Cl₂Ru=CHPh ligand environment. Strain release might overcome the otherwise slow initiation step typical for geminally-substituted alkenes. Recently, Oishi and co-workers reported a single example of catalytic cross enyne metathesis using a large excess of the geminally-substituted alkene 2-methylallyl alcohol.⁶

Reaction of methylene cyclobutane with alkyne **10A** was observed and optimized with respect to the carbene initiator. The highest reactivity in cross metathesis is typically achieved with the second generation Grubbs carbene complexes, so we focused on use of this family of Grubbs carbenes (Figure 1). The data is summarized in Table 1. In this screen, the number

not initiate at 0 °C, but good reactivity could be obtained by conducting the reaction at rt or reflux (entries 2 and 3). The phosphine-free Hoveyda–Blecher⁷ complex **4** proved to initiate at low temperature in CH₂Cl₂ and reacted well in DCE or benzene at rt. With the more active phosphine-containing bis(tolyl) complex **5**⁸ good reactivity was found, with complete conversion observed at rt (entry 7, cf. entry 2). The phosphine-free variant **6** promoted the cross-enyne metathesis at 0 °C. The Piers catalyst **7**⁹ reacted at rt (entry 9), and the newly reported Grubbs' complexes¹⁰ **8** and **9** proved highly active, promoting the cross metathesis at 0 °C in less than 5 min (entries 10 and 11).

With a good survey of catalyst efficiency, we decided to fine-tune the conditions with respect to catalyst loading and number of equivalents alkene.¹¹ At this stage, we settled on a lower reaction temperature to maintain alkene concentration for potentially longer reaction times employing fewer equivalents alkene. The results are summarized in Table 2. First, the excess

Table 1. Catalyst Screening^a

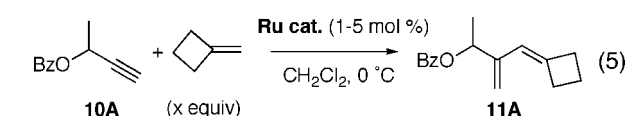


| entry | carbene complex | solvent | <i>T</i> (°C), time | % yield (NMR) ^b |
|-------|-----------------|---------------------------------|---------------------|----------------------------|
| 1 | 3 | CH ₂ Cl ₂ | 0, 5 h | NR |
| 2 | 3 | CH ₂ Cl ₂ | rt, 1 h | 93 |
| 3 | 3 | CH ₂ Cl ₂ | reflux, 15 min | 95 |
| 4 | 4 | CH ₂ Cl ₂ | 0, 15 min | 97 |
| 5 | 4 | DCE | rt, 15 min | 86 |
| 6 | 4 | PhH | rt, 15 min | 99 |
| 7 | 5 | CH ₂ Cl ₂ | rt, 20 min | 99 |
| 8 | 6 | CH ₂ Cl ₂ | 0, 20 min | 97 |
| 9 | 7 | CH ₂ Cl ₂ | rt, 20 min | 75 |
| 10 | 8 | CH ₂ Cl ₂ | 0, <5 min | 99 |
| 11 | 9 | CH ₂ Cl ₂ | 0, <5 min | 99 |

^a Conditions: 0.1 M alkyne, 0.3 M methylene cyclobutane in solvent at temperature indicated. Reactions went to complete conversion of alkyne reactant unless otherwise noted. ^b NMR yield vs mesitylene internal standard.

of alkene equivalents was kept constant at 3 equiv. With a volatile, low molecular weight alkene, we sought low temperature conditions. Temperatures lower than room temperature are not commonly used in the metathesis but are possible when using more active initiators. The parent Grubbs complex **3** did

Table 2. Refinement of Reaction Parameters^a



| entry | carbene complex | loading (mol %) | equiv | <i>T</i> (°C), time | % yield |
|-------|-----------------|-----------------|-------|---------------------|------------|
| 1 | 4 | 5 | 2 | 0, 2.5 h | 92 |
| 2 | 4 | 5 | 1.25 | 0, 4 h | 70 |
| 3 | 6 | 5 | 2 | 0, 30 h | 99 |
| 4 | 6 | 2.5 | 2 | 0, 30 h | 96 |
| 5 | 6 | 5 | 1.25 | 0, 30 h | 91 |
| 6 | 8 | 1 | 3 | 0, 1.5 h | 40 |
| 7 | 8 | 5 | 2 | 0, 3 h | 89 |
| 8 | 9 | 1 | 3 | 0, 3 h | incomplete |
| 9 | 9 | 5 | 2 | 0, 3 h | 99 |

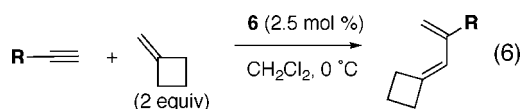
^a Conditions: 0.1 M alkyne, variable methylene cyclobutane in solvent at temperature indicated. NMR yield vs mesitylene internal standard.

alkene was decreased to 2 equiv with acceptable yield using catalyst **4**, but further reduction of alkene concentration proved deleterious to reaction yield and efficiency (entries 1 and 2). The tolyl complex **6** performed better at both lower alkene concentration and at 2.5 mol % loading (entry 4). With 5 mol % of **6**, the alkene equivalents could be reduced further (entry 5). Complex **8** did not give complete conversion at very low loading (1 mol %, entry 6) but performed adequately at 5 mol

% over a 3 h reaction time (entry 7). The tolyl complex **9** showed similar performance at 1 mol %, and a higher conversion was found at 5 mol % loading (entry 9). These data suggest that the alkene concentration can be dropped to 2 equiv while maintaining catalyst loading at 2.5–5 mol %. The alkene concentration and catalyst loading cannot be simultaneously decreased without diminishing conversion and reaction yield. From Table 2 we adopted the conditions in entry 4 as our standard conditions.

The standard conditions were applied to a range of terminal alkynes as shown in Table 3. The propargylic benzoates gave

Table 3. Reaction Scope of the Enyne Metathesis with Methylene cyclobutane^a



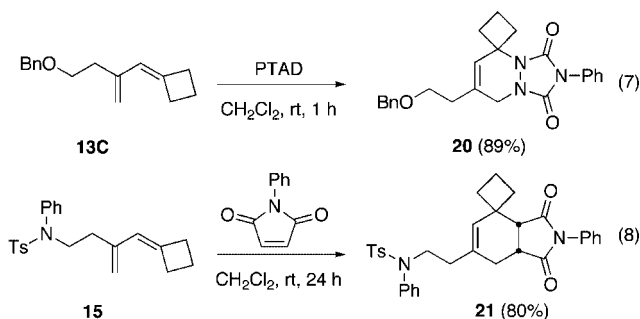
| entry | alkyne | product | % yield ^b |
|----------------|-----------------------|-----------------------|----------------------|
| | | | |
| 1 | 10A (R' = Me) | 11A (R' = Me) | 96 |
| 2 | 10B (R' = H) | 11B (R' = H) | 93 |
| | | | |
| 3 | 12A (R' = Bz) | 13A (R' = Bz) | 99 |
| 4 | 12B (R' = TBS) | 13B (R' = TBS) | 97 |
| 5 | 12C (R' = Bn) | 13C (R' = Bn) | 92 |
| 6 | | 15 | 95 |
| | | | |
| 7 | 16A (n = 1) | 17A (n = 1) | 96 |
| 8 | 16B (n = 2) | 17B (n = 2) | 95 |
| 9 ^c | | 19 | 99 |

^a Standard conditions: 0.2 M alkyne, 0.4 M alkene, 2.5 mol % of **6**, CH₂Cl₂, 0 °C, 1–3 h; 50 mol % KO₂CCH₂NC quench. (a) Isolated. (b) Performed at 0.1 M with 5 mol % **6**.

excellent results regardless of substitution (entries 1 and 2). Oxygen functionality at the homopropargylic position was also tolerated, as in typical¹² cross enyne metatheses with 1-alkenes (entries 3–5). Nitrogen functionality did not prove problematic (entry 6), and larger substituents in the propargylic position were acceptable and found to give rapid conversions under the standard reaction conditions (entries 7 and 8). Last, the homochiral amino acid derivative **18** underwent an effective cross metathesis to give the diene in quantitative chemical yield (entry 9). In summary, these reactions are very effective¹³ and high yielding using a modest amount of methylene cyclobutane, low reaction temperatures, and low catalyst loading.

The resulting 1,3-dienes are reactive in room-temperature cycloadditions. The diene products in eq 6 (Table 3) possess angle strain due to the distortion of the cyclobutane ring from ideal sp² bond angles. As a result, dienes **13C** and **15** readily undergo Diels–Alder reaction to provide the corresponding cycloadducts in excellent yield (Scheme 2).

Scheme 2. Room-Temperature Cycloadditions



In conclusion, we have shown that a strained alkene gives a highly effective cross metathesis to furnish dienes with geminal substitution at the terminal position of the diene. A wide variety of highly active second generation Grubbs carbenes were screened in the optimization study. The use of angle strain in the geminal substituents of the alkene offers a means to overcome poor reactivity of geminal alkenes and elaborates the accessible substitution patterns by catalytic enyne cross metathesis. Studies using strain as a means of achieving catalytic efficiency and extending reaction scope further are ongoing and will be reported in due course.

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Supporting Information Available: Experimental procedures and full characterization data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(11) Typically 3 equiv (or more) alkene are employed for a successful cross enyne metathesis.

(12) A notable difference in the present case is the lower reaction temperature, which is not typical of a cross enyne metathesis.

(13) Internal alkynes were found not to give the cross metathesis under the standard conditions reported here.